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Review article

Expanded carrier screening: A current perspective

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ABSTRACT

Prenatal carrier screening has expanded to include a large number of genes offered to all couples considering pregnancy or with an ongoing pregnancy. Expanded carrier screening refers to identification of carriers of single-gene disorders outside of traditional screening guidelines. Expanded carrier screening panels include numerous autosomal recessive and X-linked genetic conditions, including those with a very low carrier frequency, as well as those with mild or incompletely penetrant phenotype. Therefore, the clinical utility of these panels is still subject of debate. Priority should be given to carrier screening panels that include a comprehensive set of severe childhood-onset disorders. Psychosocial support and genetic couseling should be available prior to screening and for the return of positive results. Systems are needed to reduce the \risk of misinterpreting results. Finally, attention should be paid on the impact of expanded carrier screening on health care organizations and burden of cost.

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Background on carrier screening

Carrier screening is defined as a genetic study aimed at discovering the presence of carriers for autosomal recessive or X-linked recessive disorders in a not at *a priori* risk population, based on the personal and family genetic disease history [1].

Nowadays we count more than 2000 recessive disorders among autosomal and X-linked [2–5]. Recessive disorders affect at least 25 in 10,000 children and 1 in 100 couples are carriers, with a risk of 25% of having a child affected with an autosomal recessive genetic condition [1,5,6]. Currently, carrier screening is becoming a standard practice for individuals with a positive family history of a recessive disease [7].

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We can identify two different time intervals where carrier screening can be offered to individuals or couples: preconception screening before pregnancy, and prenatal during pregnancy. Although the prenatal screening is at present the one most performed, the preconceptional screening seems to be a better alternative to allow the parents conscious reproductive choices [7]. Newborn screening must be distinguished from carrier screening. The aim of newborn screening is to detect deseases for early treatment by testing directly the newborn. Carrier screening may allow the neonates to obtain medical care earlier than newborn screening. Carrier screening alone, however, without newborn screening would miss many affected neonates [8].

One of the major discussions about carrier scrrening is to whom it should be offered. It can be offered to individuals, usually the woman, or couples, especially when a maternal or paternal mutation is identified. Moreover, populations with different risks for heterozygous carrier frequency can be examined: low risk populations in which the test can be part of a general screening program or high risk populations because of positive family history or being a member of a particular ethnic group [2,7,9,10].

In 2013, the American College of Medical Genetics and Genomics (ACMG) published a position statement on carrier screening.[11] For a disorder to be included in carrier screening, ACMG set the following criteria: the at-risk patients and their partners identified would consider having a prenatal diagnosis; when adult-onset disorders are included in the screening panels, patients must provide consent to screening for these conditions; the causative gene(s), mutations and mutation frequencies should be known in the population being tested so that residual risk in those who test negative can be assessed; there must be a strong clinical association between mutation(s) and the severity of the disorder and compliance with ACMG quality control and proficiency testing. Genetic counseling before testing should be available and post-test genetic counseling for those with positive results is recommended. ACMG discourages including as many disorders as possible, not only because it could be not appropriated belonging to a criteria, but also because it could be unpractical for a provider to discuss each clinical condition included in a multidisease carrier screening panel [11]. Other societies such as, ACOG, the National Society of Genetics Counselors and the Society of Maternal-Fetal Medicine (SMFM) agree with ACMG criteria and reccomendations [12].

In 2017, the ACOG's Committee Opinion, Carrier Screening in the Age of Genomic Medicine, defined similar criteria and recommendations for clinicians to evaluate predefined commercial expanded carrier panels and to determine their appropriateness [13].

- Expanded carrier screening is an acceptable strategy for prepregnancy and prenatal screening
- Counseling should be offered;
- Patients should be counseled regarding residual risk with negative result;
- The reproductive partner of a woman found to be a carrier for a specific condition should be offered screening. If carriers for the same mutation are identified before pregnancy, genetic counseling is encouraged to discuss and maximize reproductive options (donor gametes, preimplantation genetic diagnosis, prenatal diagnosis);
- Given the high variability of genetic panels currently on the market, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth. Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

Nowadays, carrier screening has expanded to include a larger number of genes offered to all couples considering pregnancy or with an ongoing pregnancy. Benefits of including too many conditions in expanded panels must be weighed against harms in order to limit the psychological consequences of anxiety, stigmatization and confusion, financial expense, and clinician time and optimize the utility of the screening [14–16].

Stevens et al. established more specific criteria for inclusion of genetic conditions on expanded panels and analyzed several commercially available screening panels to evaluate if they are in line with the committee opinion [14]. On average, 73% of conditions on expanded carrier screening panels they analyzed did not match the criteria recommended by ACMG and ACOG. Terhaar et al. found that with a panel of 218 diseases, the likelihood of identifying a carrier can be as high as 36% [15].

New generation expanded carrier screening

In the age of genomic medicine, the interest in the carrier screening is growing as the genetic tests are becoming widely available and their costs are much more affordable. In the past, carrier screening has evaluated a relatively small group of mutations selected based on two main characteristics: high frequency in specific populations and severe morbidity and mortality. Currently, commercial laboratories offer test panels that screen for four to over 1700 diseases, which are not selected based on racial or ethnic background. The majority of conditions are autosomal-recessive, but some may be X-linked or autosomal-dominant single gene disorders. The rationale for expanded carrier screening is that the majority of carrier individuals have no family history of the genetic condition(s) they carry, or are not aware of their full ancestry or true ethnicity. Table 1 shows one of the preconceptional expanded carrier screening panels available on the market, including more than 700 conditions. These expanded panels include also some conditions that result in only mild to moderate health complications (e.g. factor V Leiden), have significant variations in or poorly defined pehotype (e.g. fragile X) or have onset in adulthood (e.g. BRCA1/2). The frequency of some conditions is unknown in the general population, rendering calculation of residual risk after a positive test inconclusive. Including these type of conditions in a screening panel is in direct conflict with the accepted clinical criteria for screening programs [4,6,12]. Moreover, identifying variants of uncertain clinical significance, may create patient anxiety despite counselling, which will complex and time-consuming with the inclusion of large set of disorders on the expanded screening panel. Therefore, the clinical utility of these exapanded panels is still subject to debate.

Diseases screened

In 1968, Wilson and Jungner outlined the principles for using a screening test for early disease detection [4]. These principles are still used by the World Health Organization and are still valid to justify a screening program. For reproductive screening, the aim is not of early diagnosis but to facilitate reproductive decision making.

One of the biggest challenges in the development of expanded carrier screening is to identify the appropriate criteria to uniform the test and to reduce the huge variability in current commercially available panels. The European Society of Human Genetics